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Oxidation reactions with in situ generated oxidants

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Abstract

The main achievements and future prospects of in situ oxidations are discussed, focusing on the advantages and limits of the technique. This is based on hydrogen peroxide, peracids, metal peroxo and metal oxo species, generated in situ by oxygen and a reducing agent: hydrogen, carbon monoxide, metallic iron or zinc, hydrides, aldehydes and other organic reductants. Hydrogen peroxide and hydrogen, respectively, are preferred reagents for the inherent cleanliness of their use, producing only water as the byproduct. Examples are the epoxidation of propylene by air and alkylated anthrahydroquinones, catalysed by titanium silicalite (TS-1), and the hydroxylation of alkanes and aromatics on TS-1 and on other heterogeneous catalysts loaded with noble metals. The halogenation of phenol with hydrogen/oxygen/halogenidric acid mixtures on Pd/TS-1, has also been reported. Carbon monoxide was used to replace hydrogen in in situ oxidations occurring at higher temperatures. Reducing agents other than hydrogen and carbon monoxide lead to the formation of more than stoichiometric amounts of coproducts, which add complexity to the overall process for their separation and recycle/disposal. In the in situ oxidations by Gif$^{III/IV}$ systems and by aldehyde/oxygen mixtures, large amounts of metallic wastes and carboxylic acid are co-produced, respectively, hindering their application in bulk chemicals production. Future developments might arise from the design of superior catalysts both for the in situ generation of hydrogen peroxide or peroxidic species from oxygen/hydrogen mixtures and for its subsequent efficient use. Oxygen/carbon monoxide and nitrous oxide can replace hydrogen/oxygen in oxidations at progressively higher temperatures, albeit no in situ oxidation with N_2O as yet has been reported. The general features of hydrogen peroxide and nitrous oxide are briefly compared and discussed.

1. Introduction

Oxidation processes play a significant role in chemical industry, being the basis for the production of important compounds [1]. Benefits deriving from availability, low cost and absence of wastes elect molecular oxygen as the oxidant of choice in the manufacture of bulk chemicals and whenever its use is possible. However, selectivity problems, due to the severe reaction conditions often required or to the radical nature of the reaction involved, are common obstacles to a wider use of it in synthetic chemistry. As an alternative, monooxygen donors are available as milder oxidants: hydrogen peroxide, peracids, organic hydroperoxides, inorganic and metallorganic peroxides, sodium hypochlorite, iodosobenzene, and nitrous oxide. In catalytic oxidations, these are generally characterised by good activity at moderate temperatures and, often, by good selectivity as well. However, monooxygen donors are not exempt from specific drawbacks of various nature.

– The content of active oxygen is never higher than 47 wt% (H_2O_2). It is generally close to 20 wt% or lower, burdening shipment and storage costs.

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– Major amounts of byproducts are inherent to the use of some oxidants. These require recycle/disposal and the addition of extra steps in the overall process. Even the coproduction of valuable chemicals, such as *t*-butyl alcohol or styrene in the hydroperoxide routes to propylene oxide, can occasionally represent a problem to the management of the plant, due to unbalanced market requests for the product and coproduct.
– The relatively high cost limits their use in bulk chemical production, with the exception of sodium hypochlorite.
– Supply constraints may arise when large quantities are needed. Some of them are not even available on a commercial scale.

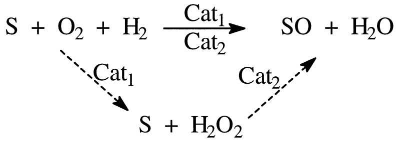
These deficiencies, while have a minor impact in fine chemistry due to high added value and relatively low volume productions, can become an impediment to the development of bulk chemical processes.

2. In situ generation of oxidants

A step towards going around some of the obstacles to the use of molecular oxygen (few active and selective catalysts) and monooxygen donors (expensive oxidants, possible market constraints) is the in situ generation of active oxygen donor species, from molecular oxygen and a reducing reagent. Half the molecule of oxygen will be effectively used for the oxidation of the substrate, the other half being discharged into a byproduct, such as water in the case of hydrogen peroxide (Scheme 1).

The examples available refer to hydrogen peroxide, metal peroxy and metal oxenoid species, peracids. Most attractive is hydrogen peroxide, on the grounds of following considerations:

– synthetic methods by direct and indirect hydrogenation of oxygen are known. Both routes are in principle compatible with the contemporary use of some known oxidation catalysts;
– hydrogen is available in most industrial plants or can be produced by well established processes;
– a rich chemistry of hydrogen peroxide, based on both homogeneous and heterogeneous catalysts, has been developed over the years;
– water is the only by-product.



Scheme 1. Oxidation of substrate S with in situ generated H_2O_2.

Metallorganic peroxy species are obtainable in situ by the reaction of corresponding metal precursors with molecular oxygen and a reducing agent or through hydrogen peroxide. Metal–oxene species are similarly obtained. Besides hydrogen, some reductants rather unpractical for commercial prospects have been used such as metallic zinc and iron or metal hydrides. The oxidations carried out by Mn–porphyrin complexes and in the so called Gif chemistry are examples of either routes.

Organic peracids have been produced in situ by two routes. Most used is the reaction of carboxylic acids with hydrogen peroxide, i.e., an indirect use of hydrogen and oxygen. A substantial difference with the direct use is that extra steps in the overall oxidation process are necessary to recover the organic acid and regenerate the peroxide from it. Reports have also appeared relative to metal catalysed oxidations with a mixture of oxygen and aldehyde. Presumably, the oxidant which is formed in situ is a percarboxylic acid.

No simple route for the in situ generation of sodium hypochlorite, iodosobenze and nitrous oxide has yet been reported nor proposed in the literature. Due to the lack of specific examples, these oxidants will not be further considered. Instead, the paper will be focused on peroxidic species. Hydrogen peroxide and titanium silicalite (TS-1) will take priority among the oxidants and catalysts, respectively, on two grounds:

– number and prospects of existing results;
– their suitability to illustrate the principles of the in situ generation of oxidants.

3. Background of in situ oxidations with hydrogen peroxide

The following discussion, albeit referred to titanium silicalite, can be extended in various degrees to other heterogeneous and, possibly, to homogeneous catalysts as well.

3.1. Routes to the in situ generation of H_2O_2

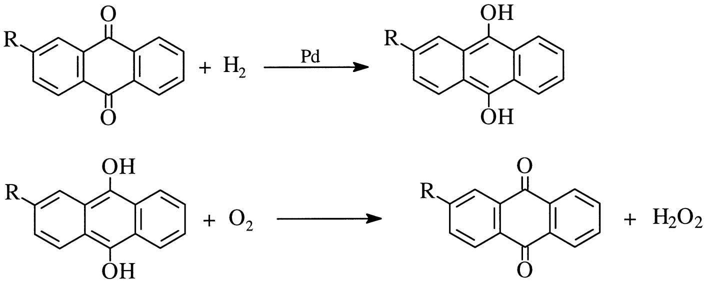
The selection of the in situ generation method presupposes its total compatibility with the oxidation catalyst and with the reagents/products involved in the overall reaction. While new specific routes to hydrogen peroxide can be looked for, the existing ones are best candidates and most obvious choice. These will be briefly examined, restricting the discussion to those aspects of possible interest for in situ oxidations. Electrochemical routes are beyond the scope of the paper and will not be considered.

Hydrogen peroxide is commercially produced by the anthraquinone process (Scheme 2) [2]. In the first stage, an alkylated anthraquinone (the carrier) is hydrogenated to its corresponding hydroanthraquinone, which in turn is oxidised with air to produce hydrogen peroxide and back again the starting anthraquinone. Before this is recycled back to the hydrogenation reactor, it is passed through purification steps to remove or chemically treat the degradation materials and to proceed to some reintegration of the working solution. In a combined oxidation process based on this route, the hydrogenation, autoxidation, separation and purification steps are expected to be retained and to undergo various modifications because of the copresence of other reagents/products. Worthy of note are also other aspects of the process. The autoxidation is run at moderate temperature, not only because it is a smooth reaction but also to prevent the degradation of anthraquinones. Unusual solvent mixtures are employed to comply with the requirements of chemical stability, good solubilizing properties for the oxidised and reduced form of the carrier, low volatility and low water affinity. A further aspect of the process is the small average size of existing plants, a point of interest for applications in high volume productions. As a matter of fact, any single installed plant capacity rarely exceeds 60,000 t/y, being difficult to say whether this is due to market or technical reasons. Other indirect routes based on an organic carrier molecule concern the autoxidation of isopropyl and of α-methyl benzyl alcohols, characterised by the high temperature of the process (90–140°C) [2,3]. The first one is the basis of a commercial process, now abandoned in western countries, while the second one is still at the development stage. The autoxidation of organic nitrogen compounds has also been studied [2].

The direct synthesis of hydrogen peroxide is pursued via the catalytic hydrogenation of oxygen, carried out on Pd-based heterogeneous catalysts in aqueous solution and in the presence of strong mineral acids and halide ions (Reaction 1) [2,4]. Worthy of note are the low temperature of the reaction, generally held in the range 0–25°C, and the overall pressure close to 100 atm, required to obtain selectivities and kinetics, respectively, of practical significance. The reaction is also carried out in aqueous/organic solvent mixtures (methanol, acetone and acetonitrile) which can be adequate for the in situ oxidation of water insoluble compounds. Although active carbons appear to be the supports of choice for the most selective and active catalysts, silica derived materials have been used as well with acceptable performances. In a few patents, homogeneous metallorganic catalysts have been claimed.

$$H_2 + O_2 \xrightarrow[H_2O/H^+/Br^-]{Pd/C} H_2O_2 \qquad (1)$$

In the selection of an in situ generation method, the anthraquinone route is favoured by various reasons. It



Scheme 2. Synthesis of hydrogen peroxide by the anthraquinone process.

is already proven on a commercial scale. The moderate operating temperature in the autoxidation step makes it suitable to oxidations in which chemically unstable derivatives are formed (e.g., epoxides). The separation of low boiling products is facilitated (e.g., lower olefin oxides). The size of the anthraquinone molecule is best suited for use with zeolitic catalysts (vide infra). On a similar argument, the routes based on isopropyl and α-methyl benzyl alcohols appear much less adequate, unless a rather different scheme is adopted for the overall process, i.e., hydrogen peroxide is preliminarly generated ex situ and then the working solution is fed to the oxidation reactor with little or no purification. Both the anthraquinone route and the autoxidation of secondary alcohols applied to in situ oxidations that occur at relatively high temperatures are questionable, because of possible oxidative degradation and other side reactions.

In oxidations in which high boiling compounds are involved, such as the hydroxylation of phenol and higher paraffins, the organic carriers (with the possible exception of isopropyl alcohol) are penalised by the consequent complexity of separation schemes. On this basis, the direct synthesis from hydrogen and oxygen has much greater potentialities, and this stimulated studies for its application in in situ oxidations. The selection of the catalyst can be guided by the relevant patent literature available in this field. It can be also prepared by supporting opportunely the active phase on the same oxidation catalyst which, in turn, is transformed into a dual site catalyst. The route is affected, however, by various drawbacks. It is not yet proven on a commercial scale. The presence of strong acids, required to get high selectivity to hydrogen peroxide, is incompatible with the epoxidation of olefins. As for the anthraquinone route, its low temperature is unsuited to those oxidations occurring quite above *RT*.

3.2. Relationship between the in situ H_2O_2 generation system and the oxidation catalyst

The in situ generating methods need also to be specifically addressed in relation to the physical and chemical features of the selected oxidation catalyst. All the routes to H_2O_2 are expected to be little compatible with catalysts constituted by soluble organometallic complexes. The absence of any restriction for the two systems from becoming into contact with each other may lead to the oxidative degradation of the organic carrier or to the inhibition of the Pd-catalyst, respectively. Nevertheless, exceptions are possible. Colloidal platinum was selected by Tabushi et al. for the in situ epoxidation of olefins with H_2/O_2 catalysed by metal porphyrin complexes [5]. The investigation, however, was finalised to mechanistic studies. It was of little interest on a preparative scale, due to the low yields and the lack of information on the chemical stability of the system.

Better chances of success are offered by in situ oxidations in which zeolitic catalysts are involved [6]. The anthraquinone route is intrinsically suitable for being used with titanosilicates having MFI (TS-1) and MEL (TS-2) structure. The average diameter of their channel systems (ca. 0.55 nm), where Ti-sites are located, prevents the diffusion of bulky molecules onto active sites and, therefore, from possible oxidative degradation or even interference with the catalytic process. The cross section of alkylated anthraquinones, being larger than 0.6 nm, fits such a requirement. Similar considerations apply as well to Ti-β (ca. 0.70 nm) and to other large pore transition metal substituted zeolites, for which a specific carrier having the right bulky substituents can be selected. Less compatible appears the anthraquinone route with mesoporous materials, in which the average porosity can be larger than 2 nm. Combining the direct synthesis of H_2O_2 on heterogeneous Pd-catalysts with micro or mesoporous oxidation catalysts fits even better the requirement of maximum separation (minimum of interference) between the two types of active sites. The noble metal can be even supported directly on titanium silicalite itself by post treatments or incorporated into it during the hydrothermal synthesis.

One further aspect to be considered is the activity of the oxidation catalyst which should be high to prevent H_2O_2 build-up in the medium and to minimise side reactions. Titanium silicalites TS-1 and TS-2 are ideal catalysts in this respect, due to their fast kinetics in dilute aqueous hydrogen peroxide solutions. In the epoxidation of propylene, initial turnover frequencies of 1–2 s^{-1} were observed at 40°C and ca. 3.4 wt% H_2O_2 [7]. On this ground, Ti-β is less promising a candidate as far as unhindered molecules are concerned [8]. Conversely, it is expectedly superior to TS-1 and TS-2 in the in situ oxidation of bulky compounds such as cyclohexane and cyclohexene, even though specific examples have not yet been disclosed.

3.3. *Choice of the solvent*

Obvious requisites are good solvent properties for both classes of reagents and stability to oxidative degradation. With zeolitic catalysts, stability might simply mean solvents constituted by sterically hindered components. A most favourable case are the oxidations with the in situ synthesis of H_2O_2 on Pd catalysts since this is compatible with the solvents generally required by Ti-zeolites, i.e., water and aqueous mixtures with methanol, acetone, and acetonitrile.

The use of methanol in the epoxidation of olefins on TS-1, and possibly on other Ti-molecular sieves, deserves a specific comment. Besides its solvent properties for reagents and products, it behaves also in this reaction as a cocatalyst by promoting the formation of the active species and taking part in the reaction mechanism (Fig. 1). Accordingly, reaction kinetics in the epoxidation of propylene comes to a maximum in the presence of methanol [9]. It follows from this observation that the addition of methanol in the solvent, even in small amount, should be beneficial to the rate of the in situ epoxidation.

4. Epoxidation with in situ generated hydrogen peroxide catalysed by TS-1

According to previous guidelines, the selection of the in situ generation method is limited to the choice of the anthraquinone carrier. Isopropyl and α-methyl benzyl alcohols demand for autoxidation conditions incompatible with the stability of the oxirane ring. The direct synthesis from H_2/O_2 mixtures occurs rather ineffectively on those catalysts able to operate under neutrality [10]. On first approach, alkylated anthraquinones currently used in industrial production of hydrogen peroxide are natural candidates for the in situ epoxidation of lower olefins. As to the catalyst, the knowledge acquired in previous studies with preformed hydrogen peroxide indicates TS-1 and TS-2 as the preferred catalysts for unhindered olefins [7,9].

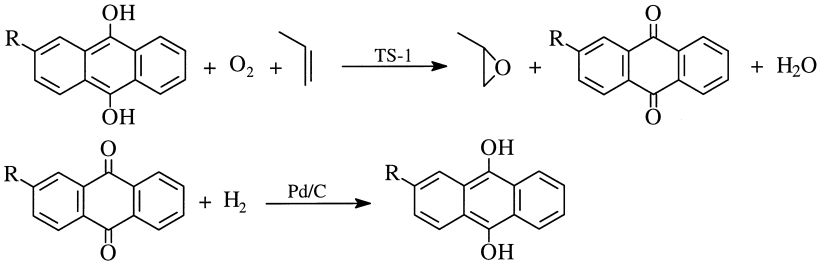
Fig. 1. Proposed active species and epoxidation mechanism [9].

4.1. *Propylene oxide*

The in situ epoxidation of propylene offers some advantages over the ex situ route. It avoids the shipment of large amounts of hydrogen peroxide when it is not available on site (on a stoichiometric basis 1 kg of H_2O_2 is required to produce 1.7 kg of propylene oxide). The low installed capacity of existing H_2O_2 plants would not constitute a possible obstacle. No dependence on external suppliers is necessary.

In Scheme 3 the epoxidation of propylene is illustrated [11]. The epoxide and water are produced by the one pot reaction of an alkylated anthrahydroquinone with molecular oxygen and propylene. The corresponding anthraquinone is subsequently hydrogenated to close the cycle of reactions. Actually, hydrogen peroxide is produced in a first step in the reaction medium, then migrates in the channel system of TS-1 to form the active species at Ti-sites (Fig. 1). This reacts with propylene in the oxygen-transfer step, as previously reported [7]. The organic carrier does not interfere in the catalytic process, prevented by its cross section larger than the diameter of TS-1 pores.

2-Ethyl- and *t*-butyl-anthraquinones were used to test the reactions of Scheme 3 [12]. Methylnaphthalene and methylisobutylcarbynol were used to dissolve the anthraquinones and their reduced form. Methanol was the third component, necessary to improve the rate of epoxidation. In Table 1 the solvent composition, quinone concentration, and yields of the reaction are reported. The yields of propylene oxide, based on starting alkylanthraquinone, were 78% and 62%, respectively, when the ethyl- or a mixture of *t*-butyl- and ethyl-substituted anthrahydroquinone were reacted at 30°C, with propylene and air in the presence of TS-1. The higher solubility of the second redox system improves the concentration of the product. Although the yields shown by Table 1 are somewhat lower than those already reported for the ex situ



Scheme 3. Epoxidation of propylene with in situ H_2O_2/TS-1.

Table 1
Epoxidation of Propylene with in situ H_2O_2[a]

Solvent Composition			Anthraquinone		PO
MEN(vol %)	DIBC (vol %)	CH_3OH(vol %)	Substituent[b]	Conc. (M)	Yield(%)
22	68	10	Ethyl[c]	0.13	78
40	50	10	Ethyl (45%) + *t*-Butyl (55%)[d]	0.22	62

[a] PO, propylene oxide; MEN, 1-methylnaphtalene; DIBC, diisobutylcarbynol [12].

[b] Substituent *R* in the 2-position of anthraquinone (see Scheme 3).

[c] Working solution 20 ml, TS-1 0.31 wt%, air 2 atm, propylene 3 atm, *T* 30°C, time 1.5 h.

[d] Reaction conditions as for c. Air 4 atm, time ca. 18 h (overnight).

synthesis of propylene oxide, these refer to non optimised experiments and are susceptible of further improvements.

A similar cycle of reactions as those of Scheme 3 was claimed by Rodriguez and Zajacek to be feasible with tetralkylammonium salts of the anthraquinone-2,6-disulphonic acid in aqueous methanol, although the epoxidation of propylene was not specifically addressed [13]. Instead, the feasibility of the epoxidation step was demonstrated on allyl alcohol, using a solution of hydrogen peroxide in which the oxidised carrier was also present. In a separate experiment the hydrogenated anthraquinone-2,6-disulphonic acid salt was shown to produce with air hydrogen peroxide, revealed by iodometric titration. It was assumed that propylene could be epoxidised through a similar sequence of reactions.

What in a sense appears to be an extension of the in situ epoxidation is disclosed in three recent patents [14–16]. Hydrogen peroxide is produced by known procedures from organic carriers and then is used, with partial or even without separation, for the epoxidation of propylene and other olefins. It is taken advantage of molecular sieve properties of Ti-zeolites to avoid the possible interference of coproducts and impurities on active sites. According to one patent, the same epoxidation solvent can be used to extract hydrogen peroxide in the conventional anthraquinone process and this solution is fed directly into the epoxidation reactor [11,14]. In a different embodiment, hydrogen peroxide is produced by the autoxidation of secondary alcohols and the resulting solution is used, in some cases after dilution with methanol, in the epoxidation step [15,16]. These process schemes do not exactly fit the idea of an in situ oxidation and require an extra reactor for the generation of hydrogen peroxide, but they can be applied when the in situ method is not practicable due to the mismatch between the conditions of hydrogen peroxide formation and substrate oxidation.

4.2. Higher olefins epoxides

The previous discussion on the in situ epoxidation of propylene may be extended to the synthesis of other low boiling epoxides as well, with only minor changes in the separation procedures. Different is the case of longer chain and functionalised olefins for which major modifications in the separation step should be expected.

5. Other oxidations with in situ generated hydrogen peroxide catalysed by TS-1

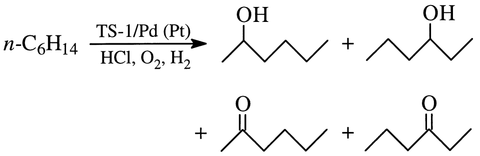
5.1. Oxidation of lower alkanes

Herron and Tolman first reported the hydroxylation of alkanes performed with a mixture of molecular hydrogen and oxygen [17]. They carried out the reaction under mild conditions at 25°C, on a 5A small pore zeolite loaded with Pd(0)/Fe(II) (Reaction 2). Hydrogen peroxide was likely formed on Pd(0) and consumed in the Fe(II) promoted hydroxylation of the alkane. The yields were understandably low, due to the radical nature of the Fe(II) reactions with H_2O_2. The turnover numbers did not exceed unity, with more than 95% of H_2/O_2 mixture ending into water. Actually, the aim of the study was to mimic monooxygenase enzymes activity with a purely inorganic system.

$$RH + H_2 + O_2 \xrightarrow{Pd(0)/Fe(II)/(5A)} ROH + H_2O \qquad (2)$$

From the standpoint of in situ oxidations, two points are worthy of note in the study. The substrate selectivity and the regioselectivity were dramatically favoured by the small pore zeolitic host. The reactivity ratios *n*-octane/cyclohexane and primary/secondary C–H in *n*-octane were >190 and 0.67, as against 0.9 and 0.05, respectively, on a similar catalyst based on amorphous silica/alumina support. Lower selectivities were also shown on medium pore zeolites. A second point of interest was the fast deactivation of the catalyst, attributed to pore plugging by organic materials and water. Their retention in the microporous system was certainly assisted by the low temperature, which indirectly contributed to the deactivation. However, this was an imposed condition, due to the decline of Pd selectivity in the generation of hydrogen peroxide over 25°C. An alternative option, based on organic carriers able to withstand higher temperatures, would probably run into separation problems.

The yields were significantly increased on TS-1 modified by a noble metal (Pd or Pt) [18]. Best TON, referred to Ti, were close to 10 and are susceptible of some improvement using excess oxygen (Reaction 3) [19].



(3)

Summaries of the oxyfunctionalisation of *n*-hexane and *n*-octane in methanol solution are provided in Table 2 [18]. Maximum yield and selectivity do not exceed 21% and 57%, respectively. These should be compared with the 86% yield (on H_2O_2) of the ex situ oxidation of *n*-hexane at 60°C [19]. The products are secondary alcohols and ketones. The latter are formed by consecutive oxidation of the corresponding alcohols on TS-1/H_2O_2 [19]. No oxidation occurs of primary C–H bonds. It is likely that the real oxidant is H_2O_2 produced in situ by the noble metal catalyst

Table 2
Oxyfunctionalisation of alkanes with H_2 and O_2, catalysed by TS-1/Pd(Pt)[a]

Alkane	Catalyst[b]	t(h)	HCl (M)	O_2(Atm)	H_2(Atm)	Conv. O_2(%)	Sel.(% on O_2)	Yields (% on O_2)
n-Hexane	TS-1/$Pd_{0.3}$	20	0.1	0.5	0.5	36	36	13
"	TS-1/$Pd_{0.3}$	24	0.01	1	8	78	14	11
"	TS-1/$Pd_{1.6}$	19	0.01	0.5	4	76	19	15
"	TS-1+Pd/C[c]	3.5	0.1	0.5	4.5	100	13	13
"	TS-1/Pt[d]	5	0.1	0.7	0.7	37	57	21
"	TS-1/$Pt_{0.3}$	19	0.1	0.5	0.5	66	5.6	3.7
n-Octane	TS-1/$Pd_{0.3}$	21	0.1	1	8	79	14	11

[a] Reaction conditions: methanol 10 ml, alkane ca.16 vol%, catalyst 12.5 g/l, *T* 25°C. The catalysts were prepared by TS-1 impregnation, drying and metal reduction under hydrogen flow at 300°C for 2 h. Nitrogen was charged when needed to rise the overall pressure to 5 atm. Alcohols and ketones were produced at β and γ positions [18]. (Beware explosion hazards. Perform the reaction in a barricade area).

[b] The lower case number indicates the metal content (wt%).

[c] Physical mixture of TS-1 (25 g/l) and Pd/C (2 g/l).

[d] TS-1/Pt*: Pt was incorporated during the hydrothermal synthesis of TS-1 [18].

from H_2 and O_2. The proposal finds support in the similarity between the selectivities of the oxidations with H_2/O_2+ TS-1+ Pd/C, H_2/O_2+ TS-1/Pd and ex situ H_2O_2+ TS-1 (Table 2 and [19]).

It is worthy of note that TS-1/Pt*, in which 0.3 wt% Pt was incorporated during the hydrothermal synthesis of TS-1, showed the highest yield, even in comparison to TS-1/Pd catalysts. This is not consistent with the patent literature on the direct synthesis of H_2O_2, almost totally based on Pd catalysts, much superior to the analogous Pt loaded ones. However, TS-1/Pt and TS-1/Pd prepared by the conventional impregnation technique showed the selectivity order expected from the literature. A likely explanation for the superior performances of TS-1/Pt* points to a higher dispersion and to a closer proximity of Pt particles and Ti-sites, i.e., of the centres that promote H_2O_2 formation and C–H bonds hydroxylation, respectively, causing a reversal of the expected trend.

The hydroxylation of *n*-hexane, with H_2 and O_2 on TS-1/Pd, was also studied by Tatsumi et al., in a biphasic water/paraffin medium [20]. The best turnover number reported was close to 1. It is not known whether such a decrease in the yields is to be attributed to the different choice of reaction conditions or to a lower activity of the catalyst. Actually, no data on Ti siting were provided by the authors relatively to the TS-1 used in the experiments. A low Ti incorporation into the MFI framework might be as well an explanation.

The kinetics, selectivity, and catalyst life in the three examples examined, do not allow to foresee any short term viable solution for the production of secondary alcohols and ketones by in situ oxidation with the H_2/O_2 mixture. Nonetheless, these indicate a direction to follow. The use of TS-1, actually a more selective and faster oxidation catalyst than Fe(II), increases the yields and TON of TS-1/Pd by one order of magnitude over the previous Pd/Fe(II)/5A.

5.2. *Hydroxylation and halogenation of aromatics*

Excluding the anthraquinone route for the reasons previously said, the hydroxylation of phenol was attempted with an equimolar mixture of H_2/O_2, under acidic conditions, using TS-1/Pd as the catalyst. To obtain reasonable kinetics and minimise deactivation phenomena, we tried the reaction at relatively high temperature, in the range 60–90°C. Not surprisingly, the presence of halogenidric acids in the oxidising medium deviated the reaction path towards the halogenation of the aromatic nucleus. Chlorophenols were formed at the *p*- and *o*-positions in a 2.5 molar ratio (Table 3) [21]. Bromination could also be carried out under analogous conditions with somewhat better results. The yields were favoured by increasing the temperature to 90°C, the HCl concentration to 0.5 M, the pressure of H_2/O_2 to above 1 atm and by using methanol as the solvent. Best yields were 33% on the starting phenol.

The reaction mechanism is not known. One possible route is the formation of H_2O_2 on Pd particles and its consumption in a second step by the oxidative halogenation of phenol. The mechanism based on the oxidation by H_2O_2 of the halogenidric acid adsorbed on the same metal particle, followed by an uncatalysed halogen attack on phenol, cannot be ruled out but it is not convincing. It is a matter of fact that Ti-sites too are somehow involved in the reaction, since the use of a mechanical mixture of TS-1 and Pd/C (longer travel

Table 3
Halogenation of phenol with H_2/O_2 mixtures and HX (X=Cl, Br) catalysed by TS-1/Pd[a]

T (°C)	HCl (M)	HBr (M)	Conv. O_2 (%)	Sel. (% on O_2)	Yields (% on phenol)
90	0.1	—	32.7	8.3	2.8
90	0.5	—	66.7	27	16.9
60	0.5	—	34.3	6.3	2.2
90	—	0.5	c	c	22
90[b]	0.5	—	c	c	33

[a] Reaction conditions: methanol 10 ml, phenol 0.2 g, catalyst 0.09 g, $H_2/O_2/N_2$ 5:5:90 (by volume), *P* 4.1 atm, time ca. 18 h (overnight). The catalyst was prepared by impregnation of TS-1 with a $PdCl_2$ solution, drying and reducing the metal under hydrogen at 60°C [21].

[b] H_2 6 atm, O_2 7 atm (Beware explosion hazards. Perform the reaction in a barricade area).

[c] Not determined.

path for H_2O_2) did not produce any halogenated material. Also, the 2.5 *p*/*o* ratio might be an indication of shape selectivity effects and therefore of the halogen attack taking place inside TS-1 channels. However, it is rather surprising that hydrogen peroxide could be generated at such unfavourable temperatures and oxidation paths not passing through H_2O_2 cannot be excluded.

Tatsumi et al., instead, carried out the hydroxylation of benzene at room temperature [20]. Phenol was formed, with the highest turnover number being close to 13. The production of halogenated derivatives was not reported, possibly due to the reluctance of benzene to undergo halogenation at such mild conditions and to the tiny concentration of phenol in the reaction mixture. Low reaction rates and fast deactivation by pore plugging, favoured by the use of two immiscible liquid phases, is one possible interpretation for the low yields, in agreement with previous discussion on the hydroxylation of paraffins.

5.3. *Ammoximation of cyclohexanone*

Likely to the epoxidation of propylene, the ammoximation of cyclohexanone is a reaction of enormous interest, providing an environmentally cleaner route to cyclohexanonoxime [22]. Although less hydrogen peroxide is required per kg of product, due to the more favourable molecular weight ratio of the reagents, an in situ oxidation route would be desirable just as for propylene oxide. However, the ammoximation reaction presents less favourable prospects. Possible chemical incompatibility with the other reagents and complexity of separation procedures do not recommend the use of organic carriers. The direct synthesis of H_2O_2 on noble metals conflicts with the basicity of the ammoximation medium. Unfortunately, no catalysts is known for the generation of hydrogen peroxide able to operate in ammonia solutions and all available information makes us to believe rather impervious an effort in this direction.

To circumvent these obstacles, various groups have devised process schemes comprising an additional section for the ex situ production of hydrogen peroxide, which is subsequently fed after little or no purification into the ammoximation reactor. Since this route falls outside the scope of the present article, it will just receive a brief outline. Roffia et al. patented the autoxidation of cyclohexanol into a mixture of cyclohexanone and hydrogen peroxide. This could be directly sent into the ammoximation step [23]. Hydrogen peroxide can be also produced by the traditional anthraquinone route, extracted by aqueous *t*-butanol and the solution used without further purification [14]. Similarly, the autoxidation of isopropanol yields a crude hydrogen peroxide solution which, after being freed from acetone and diluted with *t*-butanol, is used in the ammoximation reaction [24,25].

6. Oxidations with CO/O_2 or H_2/O_2 and noble metals catalysts

The oxidation of methane and ethane to formic and acetic acid, respectively, was achieved by Lin and Sen on Pd/C suspended in acidic aqueous solution, with oxygen/carbon monoxide mixtures at ca. 100°C [26]. Best TON referred to surface metal atoms approached 1000. Lower yields were produced replacing carbon monoxide with hydrogen. The major problems encountered were the slow kinetics and the overoxidation of primary products to eventually yield carbon oxides. Although the detailed mechanism remains unknown, the intermediate formation of hydrogen peroxide in the reaction could be established. A complex mixture of products was formed from C–H bond oxidation, CO insertion and C–C bond cleavage, when the same reaction was carried out in the presence of $RhCl_3$ in perfluorobutyric acid, at 80°C [27]. Apparently, carbon monoxide played a dual role in the reduction of oxygen and in an insertion reaction into a Rh–alkyl intermediate. Methanol and acetic acid were produced, at a rather low rate, from methane. The oxidation of ethane yielded methanol from C–C bond cleavage and ethanol and acetic acid from the oxidation of C–H bonds, while little hydroxycarbonylation to propionic acid occurred. C–C bond cleavage increased progressively with increasing carbon number and branching of the paraffin. Remarkably, alcohols appeared less prone to C–H bond oxidation than the corresponding alkanes.

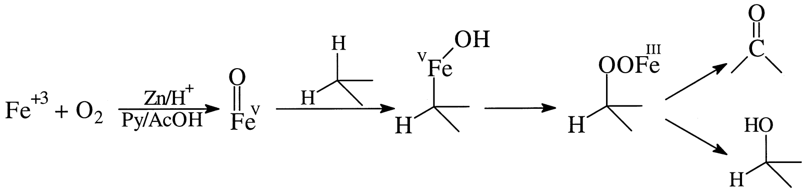
The hydroxylation of benzene to phenol was studied using hydrogen or carbon monoxide as the reductants and homogeneous or heterogeneous noble metal catalysts. Jintoku et al. used the complex of $Pd(AcO)_2$ with 1,10-phenanthroline or Pd/C to carry out the synthesis of phenol in acetic acid solution at 180°C with oxygen/carbon monoxide mixtures [28,29]. Pd–Cu catalysts supported on amorphous silica catalysed the reaction in the gas phase at ca. 100°C, in rather low yields [30,31]. These were significantly improved using precious metal catalysts supported on silica modified by various metal oxides, among which V_2O_5 was the most effective, and carrying out the reaction with H_2/O_2 at ca. 45°C [32]. The highest productivity, claimed to be of commercial level, was shown by $Pt/V_2O_5/SiO_2$. Other aromatics could be similarly hydroxylated, although with lower selectivity on hydrogen.

7. Oxidations with in situ formed metal peroxo and metal oxenoid species

Metal peroxo and metal oxenoid species can be formed directly by the reaction of metal complexes with molecular oxygen and a reducing agent, without the intermediate formation of monooxygen donors. First studies can be traced back to the work carried out by Udenfriend et al. in 1954 with the Fe^{II}/O_2/Ascorbic acid system [33]. These were later extended to comprise other low valent metal compounds (Ti^{III}, V^{III}, Cu^{I}, Sn^{II}) and other reductants [34–36]. The hydroxylation of alkanes and aromatics to corresponding alcohols and phenols by these species occurred under mild conditions. Yields were so low that any possible application was unthinkable. Accordingly, the aim of the studies was mainly the understanding of the mechanism of enzymatic oxidations, by means of simple inorganic model systems. Similar comments hold as well for the epoxidation of olefins carried out by Tabushi et al., mentioned previously [5].

Yields were significantly improved by the so called Gif system and its variations [37]. These attack paraffinic C–H bonds in the unusual order secondary>-tertiary≥primary, producing a mixture of ketones and small amounts of alcohols [38]. The ketones are mostly formed by the direct oxidation of the alkanes and less by the oxidation of intermediate alcohols. According to the authors, aliphatic C–H bonds are cleaved by an Fe^{V}–oxenoid species, producing in a first step Fe–alkyl and eventually Fe–peroxoalkyl species (Scheme 4). The corresponding ketones and alcohols are formed by the decomposition or the reduction, respectively, of the latter [38]. Various evidences were provided by the authors to support the proposed mechanism and to rule out the intermediacy of free carbon radicals in the main reaction path [37,39]. Others, instead, support a conventional free radical mechanism, denying the formation of Fe–alkyl species [40].

Relevant to present discussion are the Gif^{III} and the Gif^{IV} versions, constituted by a solution of Fe^{+2}/Fe^{+3} species in pyridine/acetic acid, molecular oxygen, and metallic iron or zinc, respectively, as the reducing agent [41,42]. An electrochemical version was also developed, in which the cathode of the cell replaced the metal in supplying the electrons [43]. Under optimal conditions, the oxidation of methylenic groups occurs smoothly at room temperature, with conversions of 10–15% and almost quantitative yields to the corresponding ketone [38]. In this context, it is also a remarkable aspect of Gif^{III} and the Gif^{IV} systems that the rate of oxidation of alkanes is faster than that of corresponding alcohols. However, on a synthetic standpoint these merits are outweighed by various negative aspects. More than stoichiometric amounts of iron or zinc is consumed in the reaction, producing huge amounts of metallic wastes. The overall rate of reaction is rather slow. Byproducts can be formed by homolytic side reactions and by overoxidation. These remarks are well exemplified by the oxidation of cyclohexane studied by Schuchardt et al.

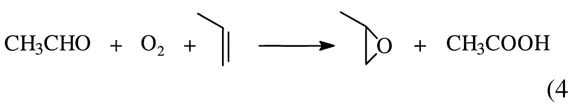


Scheme 4. Oxidation of alkanes by the Gif systems.

[44,45]. A new route to cyclohexanone based on the Gif^{IV} system resulted unpractical due to low yields on zinc (<20%), overoxidation and slow kinetics [44]. First two deficiencies could be overcome by substituting the $Zn/H^+/O_2$ reagent with hydrogen peroxide (Fe^{III}/H_2O_2, $CoAgg^{II}$ system), in consequence of which the oxidation of cyclohexane produced almost 24% yields and 91% selectivity on the oxidant, albeit at still low rate [45]. A considerable progress on kinetics could be obtained by adding a ligand to iron, leading eventually to a very different oxidation system constituted by bis(picolinato)Fe(II)/H_2O_2 ($CoAgg^{III}$ system), much more effective and cleaner than the original Gif^{IV}. With this, however, the discussion goes back on how to generate in situ hydrogen peroxide.

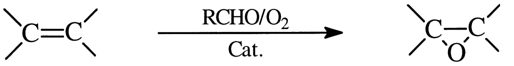
8. Oxidation with in situ formed organic peroxides

The concept of cooxidation of aldehydes and unsaturated compounds aimed at the production of corresponding epoxides with molecular oxygen is not new. It was applied in the first half of the century to unsaturated fatty acids and in the sixties to lower olefins [46–50]. The cooxidation of propylene and acetaldehyde was specifically addressed by Émanuél and coworkers, in the search of a viable alternative to the clorohydrin route to propylene oxide (Reaction 4) [47]. It was postulated that the peracid or the corresponding acylperoxy radical, formed in situ by the autoxidation of the aldehyde, could be the active epoxidizing species. Subsequent studies allowed to conclude that either mechanisms, the etherolytic and the homolytic one, were operative in various proportions, depending on the reaction conditions and the nature of the reagents [48–50]. The decisive involvement of homolytic pathways might have been a major obstacle towards sufficiently selective epoxidations.



(4)

The use of catalysts in recent years has allowed to increase the selectivity and to widen the scope of the method [51–64]. The reaction is generally carried out at room temperature in the presence of various transition metal complexes, heteropolycompounds and redox molecular sieves [51–61]. Alcohols were used in early experiments as the reducing agents, before being replaced by the more effective aldehydes [57,58]. Several olefins have been epoxidized by this route in good to excellent yields. Best results are associated with electron rich (internal and branched) olefins, suggesting an electrophilic oxidant species. A dependency on the nature of the catalyst and on the structure of the aldehyde is observed as well. Other reactions investigated are the oxyfunctionalisation of alkanes at ambient temperature [59,61,62], the Bayer–Villiger oxidation of ketones [63], the double bond cleavage [64], the enantioselective epoxidation of olefins [54] and other reactions of interest in fine chemistry.



(5)

The mechanism of reaction (5) has been little investigated and is still controversial. The inhibitory effect of phenolic compounds and the lack of stereoselectivity in the oxidations carried out in the presence of heteropolyacids or V-MCM-41, led to propose a radical chain mechanism based on acylperoxy radicals [55,56,61]. Conversely, in other oxidations performed with transition organometallic catalysts, the evidences support the intermediacy of oxometal species produced by an in situ formed oxidant [51,54,59,62,64]. From the standpoint of possible applications, a disadvantage of this route concerns the large excess of aldehyde needed, generally 2–3 times the stoichiometric amount, that ultimately yields the corresponding carboxylic acid. This is in fact the major product and might constitute the bottle neck in high volume processes, even in the case of acetic acid coproduction [62]. Less risky or even attractive might result its application in the production of fine chemicals, on condition that the use of an oxygen/aldehyde mixture offers real advantages over other oxidants. Actually, the method based on H_2O_2/carboxylic acid constitutes a clear alternative. This also possess a great advantage over the cooxidation route, i.e., the possibility of recycling the carboxylic acid, eventually consuming only hydrogen peroxide and producing water as the waste.

9. Conclusion

The examples previously discussed demonstrate the feasibility of catalytic oxidations of different substrates with in situ generated oxidants: hydrogen peroxide, metal peroxy and metal oxene species, organic peroxides. These have been used to various degrees of success and with different perspectives, depending on the specific cases. The hydrogen/oxygen mixture is the most desirable reagent and hydrogen peroxide the most desirable in situ oxidant, due to the cleanliness of the oxidation and the availability of effective heterogeneous catalysts such as the titanium zeolites. The epoxidation of propylene by this route appears to have rather promising prospects, thus encouraging further studies [11]. Other potentially attractive reactions, such as the catalysed epoxidation of lower olefins with CH_3CHO/O_2 and the oxidation of cyclohexane to cyclohexanone by the Gif^{IV} system, are eventually penalised by massive quantities of organic and inorganic co-products, respectively. It can be also noticed that the same oxidant species are generated as well by the use of preformed hydrogen peroxide or, in other words, by the use of hydrogen and oxygen as the starting reagents. A possible exception to the preferential use of the latter might be found in an application of Gif systems and aldehyde/oxygen mixtures to fine chemical production.

Recent progresses in in situ oxidations have been made possible by the discovery of effective oxidation catalysts. Examples are the titanium zeolites which are very active even in dilute aqueous hydrogen peroxide, the $Pt/V_2O_5/SiO_2$ in the hydroxylation of benzene and the transition metal complexes in the oxidations with aldehyde/oxygen mixtures. Conversely, the methods of in situ generation are substantially unchanged from previously known ex situ routes. As for the past, future developments are probably linked to the preparation of new catalysts, able to use effectively hydrogen peroxide at near *RT*. Some progresses in this direction are expected from synthetic methods able to produce heterogeneous catalysts, in which the two active phases are supported and well dispersed on the same carrier, leading to a minimisation of side reactions affecting hydrogen peroxide. However, those oxidations like ammoximation, which are incompatible with the conditions of available in situ generation, will not be feasible until new H_2O_2 routes will be designed. An alternative solution based on the use of membranes, to maintain separate the generation and the oxidation zones, would clash with the choice of suitably inert materials, with the necessity of fast transfer of hydrogen peroxide from one zone to the other, and with pore plugging phenomena by heavy organic materials and by insoluble catalysts.

The deficiencies of the H_2/O_2 route often derive from the mismatch between the optimal conditions required by the generation and the consumption steps of hydrogen peroxide. The low turnover numbers in the oxidation of alkanes were in part the consequence of conforming the overall reaction to the requirements of H_2O_2 synthesis on Pd catalysts, i.e. to the choice of *RT*, which favoured the retention of products [17]. As to the anthraquinone route, its drawbacks arise not only from the differences in the optimum reaction temperatures but also from the physical properties of the carrier and the products, which can lead to increased complexity of separation procedures. The low thermal and catalytic stability of hydrogen peroxide is also an obstacle to a wider use of it, especially in reactions which occur at relatively high temperatures. More suitable appears in this respect nitrous oxide, stable up to 400°C. It has been used for the direct hydroxylation of benzene to phenol, a reaction of great industrial interest, with remarkably high selectivity [65]. However, it is in principle an expensive reagent, and this counterbalances its merits of higher thermal stability. Nitrous oxide is in fact produced by the decomposition of ammoniun nitrate, in other words it is prepared via the ammonia synthesis, according to general reaction (6).

$$N_2 + 3H_2 + 2O_2 \longrightarrow N_2O + 3H_2O \qquad (6)$$

Two moles of ammonia, i.e. three moles of hydrogen, are needed for one atom of active oxygen. Thus, its use is more hydrogen demanding than that of hydrogen peroxide, for which a 1:1 ratio exists between hydrogen and active oxygen. Besides, no example has yet been reported of in situ preparation of nitrous oxide. The decomposition of ammonium nitrate can be considered a possible route, provided that the solution of various technical problems is found. Taking into account the deficiencies of nitrous oxide and those of other oxidants, at the moment the most promising in situ oxidation routes remain those based on hydrogen peroxide, on condition that an effective oxidation catalyst is available.

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